PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
71634-74978		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2004/000580	14.04.2004	14.04.2003
International Patent Classification (IPC) or national classification and IPC		
C07K 16/28, G01N 33/69, C12N 5/06, A61K 39/395, A61P 9/10		
Applicant		
Cartela AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 8 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☒ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☒ Box No. VI Certain documents cited
   - ☒ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.11.2004	14.07.2005
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Terese Sandström/MP Telephone No. +46 8 782 25 00

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☐ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☐ the international application as originally filed/furnished

☒ the description:

pages 1-74 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☒ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* 75-82 received by this Authority on 08.07.05
pages* _____ received by this Authority on _____

☒ the drawings:

pages 1-14 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The priority claim has been found valid. Thus, for the purpose of this opinion, the priority date is considered to be the relevant date.

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 26-27 (partially), 28-30

because:

☒ the said international application, or the said claims Nos. 26-27 (partially), 28-30 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

.../...

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box III

Claims 26-27 do not specify if the method is performed in vivo or in vitro. The remark concerns the parts relating to the method being performed in vivo. The claims are examined as if they are performed in vitro.

The method claimed in claim 28 includes a step for providing a tissue sample and a cell. The expression "providing" is open for various interpretations, and can include the actual taking of a body sample. This is considered to relate to a non-allowable method according to 67.1.(iv).

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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-27,31-44	YES
	Claims		NO
Inventive step (IS)	Claims	1-15,19-27,31-44	YES
	Claims	16-18	NO
Industrial applicability (IA)	Claims	1-27,31-44	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The present application relates to monoclonal antibodies (mabs) binding to the extracellular I-domain of the alpha10beta1 integrin. Further, it relates to methods and uses of said antibodies in identifying and selecting cells of a chondrogenic nature for treatment purposes, in particular for the identification and isolation of chondrocytes, mesenchymal progenitor cells and embryonic stem cells.

Documents cited in the International Search Report:

D1: Yednock T. A. et al.,"Alpha4beta 1 integrin-dependent cell adhesion is regulated by a low affinity receptor pool that is conformationally responsive to ligand", The Journal of Biological Chemistry, 1 December 1995, Vol. 270, No. 4, pages 28740-28750
D2: US5843436 A
D3: WO9951639 A1
D4: Database WPI, Week 200231, Derwent Publications Ltd., London, GB; Class B04, AN 2002-262913 & JP 20 01354699 A (TEIJIN LTD), 25 December 2001 (2001-12-25)
D5: WO02072030 A2.

D3 suggests mabs against the alpha10beta1 integrin, more preferably against the I-domain. However, D3 fails to disclose any examples of such mabs.

D3 is considered to be one document disclosing the closest prior art. The main difference between the claimed antibodies and D3 is that the monoclonal antibodies have actually been produced, whereas the monoclonal antibodies in D3 only have been suggested. The problem to be solved is therefore to generate the monoclonal antibodies suggested in D3.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

For assessing inventive step, two questions should be analysed; i) Would a person skilled in the art be motivated to try to do what the invention teaches, and ii) if so, would the skilled person have a reasonable expectation of succeeding. If the answer is 'no' to any of these question, the invention involves an inventive step.

The production of mabs against extracellular integrin epitopes, such as the I-domain, is problematic by routine methodology due to low or absent immunogenic capacity. Difficulties arise because such extracellular integrin epitopes are naturally 'seen' by the host immune system and hence immunisation does not provoke an immune response. It is known in the prior art that problems of producing mabs against extracellular epitopes could sometimes be overcome by administering an adjuvant with the antigen of interest. Hence, a skilled person seeking to produce mabs against the extracellular I-domain of alpha-10 would be motivated to use this known 'adjuvant' approach. However, when the present inventors tried using this 'adjuvant' approach they failed to produce mabs against the extracellular I-domain of alpha-10.

For the production of mabs against the extracellular I-domain of the integrin alpha-10 subunit, the present inventors found it necessary to use an alpha-10 knockout mouse, the immune system of which has not previously been exposed to the I-domain antigen. A skilled person would not have contemplated using such a complex, laborious and time-consuming approach. D4, which discloses the production of a mab to angiotensin II using a knockout mouse, would not lead the person skilled in the art to the claimed antibodies. Angiotensin II is not an integrin; it is a short octapeptide hormone formed by the kidneys, which circulate freely in the blood. In contrast, integrin subunits are much larger transmembrane proteins located on the surface of particular cell types. Hence, a skilled person would not expect that a methodology used successfully in D4 for the production of mabs to the short angiotensin II peptide would also be successful when applied to the production of mabs to the much larger integrin subunits.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

Moreover, even if a skilled person, on reading D3 and D4, took the inventive step of seeking to produce mabs against the I-domain of alpha-10 subunit using a knockout mouse, he/she would have no reasonable expectation of success that such an approach would work. At the best, the skilled person would have a hope to succeed; however, such a mere hope falls short of the required reasonable expectation of success required to render the claimed subject matter obvious.

It is known in the art that a high degree of sequence identity exists between different integrin alpha subunits, particularly in the extracellular I-domain. Cross-reactivity of mabs raised against a particular integrin alpha subunit for other alpha subunits is a well-recognised problem. As a consequence, a skilled person could not reasonably expect to be able to produce antibodies which are specific for just one alpha subunit.

In this regard, it is significant that the use of a knockout mouse by the present inventors resulted in the production of only one hybridoma clone (out of 29 positive clones) capable of producing mabs with specificity for the I-domain of alpha-10. Furthermore, in a related experiment by the inventors, the same knockout mouse approach failed to produce any hybridoma clones capable of producing a mab with specificity for the I-domain of alpha-11 subunit. In such circumstances, it is apparent that a skilled person could not, and would not, have a reasonable expectation of success.

In addition, it is significant that no anti-alpha-10 mabs were disclosed prior to the present invention, even though D3 was published over three years before the present application was filed. In this fast moving field of biotechnology, three years represent a very long time; if the production of mabs against the I-domain of alpha-10 were obvious, method for their production would have been published much sooner.

D5 describes different variants of the integrin alpha A-domain (also called the I-domain), e.g. from the alpha10 integrin, and suggests the use of such for the generation of I-domain specific monoclonal antibodies. (Page 3, line 21-page 4, line 8; figure 5; table 2; table 4; page 18, line 25-page 19, line 2; page 21, line 10-page 22, line 12; claims 52-55.)

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

However, D5 also fails to disclose any examples of such mabs. It is merely stated in D5 that such antibodies 'can be generated using standard methods' (see page 21, lines 13-16).

It is readily apparent from the above discussion that 'standard methods' for the production of mabs against an extracellular epitope of integrin alpha chains would not be successful.

To summaries, the claimed monoclonal antibodies against the extracellular I-domain of alpha-10 are considered to involve an inventive step in view of the prior art.

In view of the present description, it seems as if only some mesenchymal stem cells as well as embryonic stem cells express the alpha10 integrin while all chondrocytes do. In view of that, claims 16-18 relate to a population of chondrocytes in general (since any such population would fulfil the requirement of being obtainable by the claimed methods). Such a population can not be considered to include an inventive step.

D1 and D2 disclose monoclonal antibodies, which specifically bind to the beta1 integrin. (D1: page 28741, column 1, paragraph 3-column 2, paragraph 1; D2: column 5, lines 40-65; column 6, lines 16-41; column 13, line 1; column 17, lines 52-53.)

D1 and D2 are considered to disclose the general state of the art.

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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO03101497 A1	11.12.2003	11.04.2003	12.04.2002
WO03106492 A1	24.12.2003	12.06.2003	14.06.2002

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

EU Directive 98/44EC of July 1998 of the legal protection of biotechnological invention has been implemented in the national law of several countries. Article 6 of the directive excludes the industrial use of human embryos. Claims 9, 20-22, 25 and 27 relate to the use of embryonic stem cell as well as subpopulations of embryonic stem cells per se. The scope of the claims also includes human embryonic stem cells. Be aware that some countries may not allow this type of claims.

Claim 44 seems to refer to the wrong claims.

AMENDED CLAIMS

1. A monoclonal antibody capable of binding to a protein which is specifically recognized by the monoclonal antibody produced by the hybridoma deposited at the Deutsche Sammlung von Microorganismen und Zellkulturen GmbH under the accession number DSM ACC2583 or an **antigen-binding** fragment thereof, **wherein the antibody or fragment binds specifically to the extracellular I-domain of the integrin alpha10 chain.**

2. **A monoclonal antibody or a fragment thereof according to claim 1 wherein the antibody or fragment is of murine origin.**

3. **A monoclonal antibody or a fragment thereof according to claim 1 wherein the antibody or fragment is humanized.**

4. **A monoclonal antibody or a fragment thereof according to any one of claims 1 to 3 wherein the fragment is selected from the group consisting of Fv, Fab, Fab', $F(ab')_2$ and single antibodies.**

5. **A monoclonal antibody or fragment thereof according to claim 1 or 2 wherein the antibody is produced by the hybridoma cell line deposited at the Deutsche Sammlung von Microorganismen und Zellkulturen GmbH under the accession number DSM ACC2583.**

6. A hybridoma cell line deposited at the Deutsche Sammlung von Microorganismen und Zellkulturen GmbH under the accession number DSM ACC2583.

7. A method for isolating a population of mammalian mesenchymal stem cells, the method comprising the steps of

   a) providing a cell suspension comprising mammalian mesenchymal stem cells,
   b) contacting the cell suspension in a) with a monoclonal antibody or a fragment **according to any one of claims 1 to 5**, under conditions wherein said monoclonal antibody or a fragment thereof forms an antibody-antigen complex with the extracellular domain of integrin alpha10beta1,
   c) separating cells binding to the monoclonal antibody or a fragment thereof in b), and optionally
   d) recovering cells binding to the monoclonal antibody or a fragment thereof in

c) from said antibody or a fragment thereof,
thereby producing a population of mammalian mesenchymal stem cells, optionally free from said antibody or a fragment thereof.

8. A method for isolating a population of mammalian chondrocytes, the method comprising the steps of

a) providing a cell suspension comprising chondrocytes,
b) contacting the cell suspension in a) with a monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5**, under conditions wherein said monoclonal antibody or a fragment thereof forms an antibody-antigen complex with the extracellular I-domain of integrin alpha10beta1,
c) separating cells binding to the monoclonal antibody or a fragment thereof in b), and optionally
d) recovering cells binding to the monoclonal antibody or a fragment thereof in c) from said antibody or a fragment thereof,
thereby producing a population of chondrocytes, optionally free from said antibody or a fragment thereof.

9. A method for isolating a sub-population of mammalian ES cells, the method comprising the steps of

a) providing a cell suspension comprising ES cells,
b) contacting the cell suspension in a) with a monoclonal antibody or a fragment thereof binding **according to any one of claims 1 to 5**, under conditions wherein said monoclonal antibody or a fragment thereof forms an antibody-antigen complex with the extracellular I-domain of integrin alpha10beta1,
c) separating cells binding to the monoclonal antibody or a fragment thereof in b), and optionally
d) recovering cells binding to the monoclonal antibody or a fragment thereof in c) from said antibody or a fragment thereof,
thereby producing a population of chondrocytes, optionally free from said antibody or a fragment thereof.

10. The methods according to any of claims 7-9, wherein the monoclonal antibody or a fragment thereof is linked to a solid phase.

11. The methods according to any of claims 7-10, wherein the solid phase are beads.

12. The methods according to any of claims 7-11, wherein the mammalian cells are

human cells.

13. The methods according to claim 7-12, wherein the mammalian cells are murine cells.

14. A population of mammalian mesenchymal stem cells obtainable by the methods according to any of claims 7, and 9-13.

15. The population of mammalian stem cells according to claim 14, being human mesenchymal stem cells.

16. The population of mammalian stem cells according to claim 14, being murine mesenchymal stem cells.

17. A population of mammalian chondrocytes obtainable by the methods according to any of claims 8, and 10 -13.

18. The population of mammalian chondrocytes according to claim 17, being human chondrocytes.

19. The population of mammalian chondrocytes according to claim 17, being murine chondrocytes.

20. A subpopulation of mammalian ES cells obtainable by the methods according to any of claims 7, and 9 -13.

21. The population of mammalian **ES cells** according to claim 20, being human chondrocytes.

22. The population of mammalian **ES cells** according to claim 20, being murine chondrocytes.

23. A method for detecting a mesenchymal stem cell in a sample, the method comprising the steps of

a) providing a sample cell suspension comprising a mesenchymal stem cell,
b) contacting said sample cell suspension with a monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5,**
c) incubating the sample cell suspension and the monoclonal antibody or a fragment thereof under conditions wherein said monoclonal antibody or a

fragment thereof forms an antibody-antigen complex with the extracellular domain of integrin alpha10beta1 on a mesenchymal stem cell,

d) optionally adding a second labelled antibody or a fragment thereof to the sample, wherein the second antibody or a fragment thereof binds to the monoclonal antibody or a fragment thereof in b)

e) detecting the monoclonal antibody or a fragment thereof bound to the extracellular domain of integrin alpha10beta1of the sample b), or optionally detecting the second labelled antibody or a fragment thereof in c) bound to the monoclonal antibody or a fragment thereof,

thereby detecting the mesenchymal stem cell.

24. A method for detecting a chondrocyte in a sample, the method comprising the steps of

a) providing a sample cell suspension comprising a chondrocyte,

b) contacting said sample cell suspension with a monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5,**

c) incubating the sample cell suspension and the monoclonal antibody or a fragment thereof under conditions wherein said monoclonal antibody or a fragment thereof forms an antibody-antigen complex with the extracellular domain of integrin alpha10beta1 on a chondrocyte,

d) optionally adding a second labelled antibody or a fragment thereof to the sample, wherein the second antibody or a fragment thereof binds to the monoclonal antibody or a fragment thereof in b)

e) detecting the monoclonal antibody or a fragment thereof bound to the extracellular domain of integrin alpha10beta1of the sample b), or optionally detecting the second labelled antibody or a fragment thereof in c) bound to the monoclonal antibody or a fragment thereof,

thereby detecting the chondrocyte.

25. A method for detecting an ES cell in a sample, the method comprising the steps of

a) providing a sample cell suspension comprising an ES cell,

b) contacting said sample cell suspension with a monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5,**

c) incubating the sample cell suspension and the monoclonal antibody or a fragment thereof under conditions wherein said monoclonal antibody or a fragment thereof forms an antibody-antigen complex with the extracellular domain of integrin alpha10beta1 on an ES cell,

d) optionally adding a second labelled antibody or a fragment thereof to the

sample, wherein the second antibody or a fragment thereof binds to the monoclonal antibody or a fragment thereof in b)

e) detecting the monoclonal antibody or a fragment thereof bound to the extracellular domain of integrin alpha10beta1of the sample b), or optionally detecting the second labelled antibody or a fragment thereof in c) bound to the monoclonal antibody or a fragment thereof

thereby detecting the ES cell.

26. A method for blocking the binding of a chondrocyte to an extracellular matrix molecule (ECM), the method comprising the steps of

a) providing a monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5,**

b) contacting said monoclonal antibody with said chondrocyte under conditions wherein said monoclonal antibody or a fragment thereof forms an antibody-antigen complex with the extracellular domain of integrin alpha10beta1

c) incubating the antibody-antigen complex in b) above, thereby blocking the binding of a chondrocyte to said ECM molecule.

27. A method for modulating the signalling of alpha10beta1 on a mammalian mesenchymal stem cell, ES cell or a chondrocyte, the method comprising the steps of

a) providing a monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5,**

b) contacting said stem cell or chondrocyte under conditions wherein said monoclonal antibody or a fragment thereof forms an antibody-antigen complex with the extracellular domain of integrin alpha10beta1 on said cells, and

c) incubating said antibody-antigen complex,

thereby modulating the signalling of alpha10beta1 on a human mesenchymal stem cell, ES cell or a chondrocyte.

28. A method for detecting the expression of integrin alpha10beta1 in a tissue sample or on a cell surface, the method comprising the steps of

a) providing a tissue sample or a cell,

b) providing a monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5** in the tissue sample or cell,

c) incubating the tissue sample or cell and the monoclonal antibody or a fragment thereof under conditions wherein said monoclonal antibody or a

fragment thereof forms an antibody-antigen complex with the extracellular domain of integrin alpha10beta1,

d) optionally adding a second labelled antibody or a fragment thereof to the sample, wherein the second antibody or a fragment thereof binds to the monoclonal antibody or a fragment thereof in b),

e) detecting the monoclonal antibody or a fragment thereof bound to the extracellular domain of integrin alpha10beta1of the sample b), or optionally detecting the second labelled antibody or a fragment thereof in c) bound to the monoclonal antibody or a fragment thereof.

29. A method for in vivo imaging the expression of the integrin alpha10beta1 in a mammal, the method comprising the steps of

a) providing a mammal,

b) providing an monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5**, and wherein said monoclonal antibody or a fragment thereof optionally are conjugated,

c) administering the monoclonal antibody or a fragment thereof to the mammal so as to allow the antibody or a fragment thereof to bind to the extracellular I-domain of integrin alpha10beta1of cells in said mammal,

d) optionally adding a second labelled antibody or a fragment thereof to the sample, wherein the second antibody or a fragment thereof binds to the monoclonal antibody or a fragment thereof in c),

e) detecting the monoclonal antibody or a fragment thereof bound to the extracellular I-domain of integrin alpha10beta1of said cells in c), or optionally detecting the second labelled antibody or a fragment thereof in d) bound to the monoclonal antibody or a fragment thereof, and

f) creating an image of the detected antibody or a fragment thereof,

thereby imaging the expression of integrin alpha10beta1 on cells in a mammal in vivo.

30. The method according to claim 29, wherein the extracellular I-domain of integrin alpha10beta1 is on a cell in an atherosclerotic plaque in a blood vessel.

31. A composition comprising a monoclonal antibody **or fragment according to any one of claims 1 to 5**.

32. The composition according to claims 31 wherein the monoclonal antibody or a fragment thereof further comprises a detectable label.

33. An administration vehicle comprising a monoclonal antibody **or fragment according to any one of claims 1 to 5.**

34. An administration vehicle according to claim 33, comprising a monoclonal antibody **or fragment according to any one of claims 1 to 5,** a pharmaceutical acceptable carrier, and a pharmaceutical acceptable drug affecting joint diseases or atherosclerosis.

35. Use of a monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5,** for the preparation of a pharmaceutical composition for the treatment of musculoskeletal diseases, arthritis or atherosclerosis.

36. Use of a monoclonal antibody or a fragment thereof **according to any one of claims 1 to 5** for the preparation of a pharmaceutical composition for gene therapy treatment of musculoskeletal diseases, arthritis or atherosclerosis.

37. The use according to claim 36, wherein the pharmaceutical composition comprises an adenovirus for gene therapy treatment of arthritis.

38. A kit comprising a monoclonal antibody **or fragment thereof according to any one of claims 1 to 5.**

39. The kit according to claim 38, wherein the monoclonal antibody or a fragment thereof is bound to a solid phase.

40. The kit according to any of claims 38-39, wherein the monoclonal antibody or a fragment thereof comprises a detectable label.

41. A kit comprising a hybridoma cell line according to claim 7, and a cell culture medium for said hybridoma cell line.

42. A method for making a monoclonal antibody according to Claim 1, the method comprising the steps of

a) immunising and boosting an alpha-10 knock-out mouse with recombinant alpha-10 I-domain;

b) fusing the spleen cells from the immunised mouse with immortalised cells to create hybridoma cells; and

c) culturing the hybridoma cells and isolating the antibodies produced thereby.

43. A method according to Claim 42 wherein the immortalised cells are NSO cells.

44. A monoclonal antibody produced by a method according to Claim 41 or 42.